Therapeutic Attempts in Idiopathic Infertility

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Abstract

About 30–60% of men with impaired fertility suffer from idiopathic infertility for which there are no rational therapeutic approaches. Nevertheless, numerous pharmaceuticals and procedures have been and are still being used, often over long periods of time and frequently in combination or in sequence, which are summarized as empirical therapy. Here, the postulate of evidence-based medicine for randomized controlled trials proves to be particularly important, and it is according to these strict standards that the various therapeutic procedures are critically evaluated in this chapter. While results in individual studies are often promising, further evaluation in meta-analyses is usually less clear. In summary, none of these drugs or procedures is evidence-based and fail to be recommended in guidelines for male infertility.

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39.1 Definition and Incidence of Idiopathic Infertility

About 30–60% of men with impaired fertility suffer from **idiopathic infertility** (Tüttelmann and Nieschlag 2009; Punab et al. 2017). Idiopathic infertility represents a diagnosis of exclusion and may be made only after other fertility-disrupting causes have been ruled out. Seminal parameters may be subnormal and elevation of FSH may indicate spermatogenic disorder. However, testicular biopsy does not provide further diagnostic information. Histologically, incomplete spermatogenesis or partial SCO syndrome is often found. These patients form the largest group of men attending the fertility consultation.

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The collective diagnosis of **idiopathic infertility** conceals a multitude of different pathogenetic mechanisms. Their elucidation is one of the most important and exciting tasks of andrology and may finally allow rational therapy to overcome the causative disorders of idiopathic infertility. New approaches can be expected mainly from research on the genetic and biological control of spermatogenesis, the action of gonadotropins and sex hormones at the molecular level, and the biology of gametes. Examples of such research areas include microdeletions on the Y chromosome, CFTR mutations in congenital bilateral aplasia of the vas deferens (CBAVD), and androgen receptor pathology.

It should be emphasized that the term idiopathic infertility is used differently in andrology and gynecology. The gynecologist speaks of idiopathic infertility of a woman when, despite intensive diagnostics, no pathological findings can be found in the patient explaining the unfulfilled desire for children. In this case, it is rather a case of unexplained infertility (see Chap. 41). In idiopathic infertile men, on the other hand, while a pathological condition can be found, there is (as yet) no causal explanation for it and consequently, no rational therapy.

Even though there are no clear pathophysiological concepts as to why a particular drug should be effective in idiopathic infertility, numerous pharmaceuticals have been and continue to be used, often over long periods of time, often in combination or in sequence, which are summarized here as **"empiric therapy."** Here, the postulate of **Evidence-Based Medicine for randomized controlled trials** proves particularly appropriate, and it is according to these strict standards that the drugs below are critically evaluated.

Empiric therapies were long practiced in andrology until their lack of effectiveness was verified in randomized controlled trials. Since temptations to use these forms of therapy flare up time and again, previous results have been summarized here to discourage the reader from unnecessary attempts at therapy. For this reason, older work is also listed. However, the number and types of empirical therapeutic approaches have changed since ICSI has partially taken over the role of empiricism (see Chap. 1).

39.2 Empirical Therapy

39.2.1 Gonadotropins: hCG/hMG/rFSH

FSH and LH are critical regulators in human spermatogenesis. In hypogonadotropic hypogonadism, administration of these gonadotropins (or FSH and hCG) is indicated and their effect on spermatogenesis is scientifically proven and appropriately recognized. But what is the **effect of FSH and/or hCG in men with impaired spermatogenesis** and normal FSH levels? In Germany, the application of FSH at physiological FSH levels is not approved.

Although in some single studies, an improvement of sperm parameters, DNA fragmentation index (DFI) or pregnancy rate after FSH treatment could be shown in idiopathic infertile men, in other older studies this could not be confirmed (Kamischke et al. 1998; Foresta et al. 2005; Paradisi et al. 2006; Simoni and Santi 2020). The **quality of studies is very heterogeneous** and comparisons between papers are difficult, mainly due to different: selection criteria in the study population, type of gonadotropins (rFSH vs. urinary-derived), duration of therapy and endpoints (pregnancy vs. sperm parameters).

A **2013 Cochrane analysis** analyzed six randomized controlled trials comparing the effect of gonadotropins to placebo or to no treatment in idiopathic infertility (Attia et al. 2013). Initially, there was a significant increase in the occurrence of spontaneous pregnancies (OR 4.94 [2.13–11.44; moderate level of evidence] and live births (OR 9.31 [1.17–73.75; very weak level of evidence]). However, the authors themselves concluded that due to the small study size and small number of participants ($n = 456$), the evidence is very weak and no definitive recommendations could be derived (Attia et al. 2013). In a 2015 meta-analysis that analyzed 15 studies (randomized and nonrandomized) for the effect of FSH or hMG (human menopausal gonadotropin) treatment, the authors came to a similar conclusion: partner pregnancy rates were higher among idiopathically infertile men who received FSH (Santi et al. 2015). This observation held true for spontaneous pregnancies (OR 4.5 [2.17–9.33]) as well as pregnancies after ART (OR 1.6 [1.08–2.37]). The results were independent of the type of FSH and duration of treatment. Effect size calculation showed that ten couples would need to be treated to achieve pregnancy. Interestingly, in a sub-analysis concerning sperm parameters, only sperm concentration showed a significant increase, other parameters remained unchanged. In the most recent meta-analysis, which included a total of five studies investigating the effect of FSH in oligozoospermic males with FSH serum levels <12 IU/L, a dose-dependent effect was found with respect to sperm concentration, total sperm count, and motility. This effect was independent of the preparation of FSH (hpFSH vs. rFSH) (Cannarella et al. 2020).

Overall, these are promising results, yet sensitive parameters such as FSH serum level and total sperm count are not sufficient to predict FSH treatment response.

Predictive markers are needed to target FSH therapy and to show the positive impact on the properly selected group (Santi et al. 2015; Behre 2019; Schubert et al. 2019). Here, pharmacogenetic approaches seem to be the most promising (Simoni and Casarini 2014; Busch et al. 2015; Schubert et al. 2019; Casarini et al. 2020; Simoni and Santi 2020). There are a few studies that have taken an FSH-based pharmacogenetic approach in idiopathic infertile men (Ferlin et al. 2011; Selice et al. 2011; Simoni et al. 2016; Casamonti et al. 2017). Patient

cohorts were subgrouped with respect to a genetic variant (single-nucleotide polymorphism—SNP) in the FSH receptor or in the FSHB gene and assigned to gonadotropin therapy accordingly. However, again, due to divergent selection criteria, treatment duration, and different endpoints, no reliable conclusions or consequences can be derived (Schubert et al. 2019). Fundamentally prospective, randomized, and placebo-controlled studies will be needed to clarify the question of FSH efficacy on a subgroup of idiopathically infertile men.

In the guideline on the management of oligoasthenozoospermia, the European Academy of Andrology (EAA) **recommends FSH administration as a potential therapeutic option** in normogonadotropic patients with idiopathic oligozoospermia or OAT, but the level of evidence is reported as very low (Colpi et al. 2018). In the European Association of Urology (EAU) Guidelines on Male Infertility, the authors stipulate that no clear recommendation for gonadotropin treatment can be made to men with idiopathic infertility (Jungwirth et al. 2012).

Given the good success rate of hCG/hMG therapy in achieving pregnancy in hypogonadotropic hypogonadism, since the early 1960s this treatment has also been tried in patients with normogonadotropic fertility disorders. A **placebo-controlled, prospective, randomized study** then showed that in patients with normal serum concentrations of LH, FSH, and testosterone and spermatozoa concentrations below 10 million/mL, treatment with hCG/hMG did not improve ejaculate parameters or increase pregnancy rates compared with the placebo group (Knuth et al. 1987). Moreover, this study highlighted the placebo effect, since improvements in ejaculate parameters were also observed in the double-blind treated placebo group. Accordingly, normogonadotropic idiopathic infertility is not an indication for hCG/hMG therapy.

39.2.2 Antiestrogens and Aromatase Inhibitors

The **antiestrogens (clomiphene citrate, tamoxifen**) cause an increase in GnRH via blockade of estrogen receptors in the hypothalamus and pituitary. **Aromatase inhibitors (anastrozole**) inhibit the conversion of androgens to estrogens. Assuming that the increase in LH and FSH leads to an improvement in spermatogenesis, antiestrogens and aromatase inhibitors are also used in idiopathic infertility.

39.2.2.1 Antiestrogens

Regarding the benefit of **tamoxifen** when used in idiopathic infertile men, there are some older meta-analyses and reviews. The earlier analyses failed to show a significant effect of antiestrogens on pregnancy rates (Kamischke and Nieschlag 1999; Vandekerckhove et al. 2005). A 2013 meta-analysis showed that SERMs (Selective Estrogen Receptor Modulators) increased sperm concentration, motility, and pregnancy rate (Chua et al. 2013). The drawback of this meta-analysis, which also chose pregnancy rate as the primary endpoint, is the relatively small number of studies (n = 11) and the associated small cohort size (n = 903). The pooled OR showed a 2.4-fold increased probability of pregnancy occurrence when the male idiopathic infertile partners were treated with antiestrogens compared with the control group. The calculation showed a **number needed-to-treat of n = 10 couples**. In a subgroup analysis comparing clomiphene 50 mg with tamoxifen 20–30 mg/day, no drug was shown to be more effective in comparison (Chua et al. 2013).

The low side effect profile and comparatively low cost may, according to some authors, support therapy for 3–6 months, but not longer than 12 months. The effect on FSH and testosterone was also significant, leading to the conclusion that the therapy can be used in idiopathic infertile men with testosterone deficiency (Whitten et al. 2006). It is an off-label use. The authors of the EAA guidelines on the management of OAT are not specific about recommending therapy with antiestrogens or aromatase inhibitors, and the **level of evidence is considered very low** (Colpi et al. 2018). Similarly, the authors of the EAU guideline on male infertility refrain from a clear recommendation regarding the use of antiestrogens (Jungwirth et al. 2012).

39.2.2.2 Aromatase Inhibitors

Among aromatase inhibitors (AIs), **testolactone** (steroidal; no longer approved in the U.S.) and **anastrozole** and **letrozole** (nonsteroidal) are the main drugs found in the literature. AIs have the advantage of increasing endogenous testosterone without altering estrogens. These drugs are approved for metastatic breast cancer; their use in idiopathic infertile men is an off-label treatment. Some men with severely impaired spermatogenesis have an increased testosterone/estradiol (T/E2) ratio due to increased aromatase activity, so the use of inhibitors would be a consistent approach (Pavlovich et al. 2001).

In a recent systematic review and meta-analysis, randomized and nonrandomized studies from the past 30 years were examined for the efficacy of AI on testosterone concentrations, T/E2 ratio, and sperm concentration in hypogonadal OAT patients. With regard to testosterone levels, all studies analyzed showed an increase of 48.5% (del Giudice et al. 2020). In the effect on T/E2 ratio, an increase of 227% (five studies included) and in the analysis of sperm concentration, an increase of 116% (three studies included) was observed. No improvement was detected in patients with azoospermia (del Giudice et al. 2020). Another study compared the efficacy of anastrozole and letrozole; no significant differences in the effect on testosterone level and sperm concentration were detected between the two AIs (Raman and Schlegel 2002).

Because of the divergent statistical evaluations of different sperm parameters (the main conclusion of the meta-analysis is that AIs have an effect on testosterone levels (del Giudice et al. 2020). Therefore, the EAA guidelines for the management of OAT patients cannot currently recommend the use of aromatase inhibitors (Colpi et al. 2018). A statement on pregnancy rates cannot be made. Overall, AIs could be considered as well-tolerated, apart from a temporary increase in liver enzymes. It can be concluded that men with a low testosterone level and a low T/E2 ratio might benefit from an AI, presumably rather than from a preparation from the SERM group (Schlegel 2012).

39.2.3 Antioxidants, Diets, and Supplements with Antioxidant Effects: Vitamins, Folic Acid, Zinc, Carnitine, and Others

As in other fields of medicine, pathological phenomena in andrology are associated with oxygen-free radicals. **Oxidative stress** is discussed as a **cause of fertility disorders** (Tremellen 2008) and antioxidants such as some vitamins are used for therapy. While oxidative stress can negatively affect spermatogenesis and sperm maturation, oxygen-free radicals in physiological concentrations are also required for normal sperm function (Aitken 1995). For example, a negative correlation has been shown between the rate of fertilization in vitro and the capacity of sperm to destroy oxygen-free radicals (Yeung et al. 1996).

Antioxidants prevent or delay the oxidation of biologically relevant molecules; this is done by scavenging free radicals or by chelation (Valko et al. 2006). Oxidative stress can affect fertility through two mechanisms: first, by **damaging the sperm membrane** and second, by apoptosis and direct **alteration of sperm DNA** (Kodama et al. 1997; Lewis et al. 2013). The latter can be canceled by superimposition of normozoospermia, limitations in DNA fragmentation (DFI) can be detected by various tests. Some authors consider DFI determination as an elementary part of diagnostics.

Some vitamins and trace elements have an antioxidant effect and, like substances with a direct antioxidant effect, are part of dietary supplements. Table 39.1 shows a selection of these substances, with their corresponding antioxidant properties and natural occurrence. Further information can be found in the Cochrane Review (Smits et al. 2019). Often, these substances are part of the therapeutic desire of idiopathic infertile men who are denied causal therapy due to a lack of etiological factors.

Considering the many beneficial properties of antioxidants, dietary supplementation with these substances seems logical to improve fertility.

Of a large number of mostly uncontrolled clinical trials with diverse individual antioxidants and their combinations, a recent Cochrane Review lists 61 randomized clinical trials with **arginine, L-carnitine, coenzyme Q10, N-acetyl cysteine, carotenoids, micronutrients (calcium, magnesium, selenium, zinc), vitamins (B6, B12, E, and C), and myo-inositol**, which were studied as single substances or in combination (Smits et al. 2019). The vast majority of studies exclusively examine the effect of antioxidants on ejaculate parameters and/or DNA fragmentation, and only a few studies examine clinical pregnancy rate ($n = 12$) or live birth rate ($n = 7$). Overall, antioxidants show potential improvement in DNA fragmentation, sperm concentration, and sperm motil-

Table 39.1 Overview of antioxidants, trace elements, and other substances with antioxidant activity (from Smits et al. 2019)

	Substance	Antioxidant properties	Occurrence	References
Antioxidants	**Arginine**	Radical scavenger	Meat, dairy products, nuts	Appleton (2002)
	Coenzyme Q10	Ubiquinol (reduced form) prevents protein and DNA oxidation	Meat, fish, nuts	Littarru and Tiano (2007)
Trace elements	**Folic acid (vitamin B9)**	In synthetic form radical scavenger	Green vegetables, liver, fruits	Joshi et al. (2001)
	Zinc	Strong antioxidant effect; involved in testicular development and phys. sperm function	Meat, grains, seeds	Colagar et al. (2009)
	Vitamin E (bioactive: Tocopherol A)	Antioxidant effective in membrane damage induced by oxidation	Vegetable oil	Traber and Atkinson (2007)
	Vitamin C (ascorbic acid)	Reduces DNA damage as a radical scavenger	Fruit, vegetables	Padayatty et al. (2003)
Substances with antioxidant properties	**Myo-inositol**	Increases endogenous antioxidant enzymes	Self-synthesis possible by vitamin B5 and glucose	Condorelli et al. (2017)
	Resveratrol	Enhances antioxidant effects	Grapes, berries, wine	Branco et al. (2010)
	Vitamin B complex (B1/2/12)	Involved in homocysteine metabolism, homocysteine has prooxidant properties	Meat, beans, potatoes, bananas	Hankey and Eikelboom (1999)
	Vitamin D	Antioxidant property via activation dismutase	Sun-induced synthesis	Dorota Halicka et al. (2012)

ity in the overall Cochrane analysis, although the marked heterogeneity of the studies and high likelihood of bias allow only low to very low evidence for this statement (Smits et al. 2019).

Furthermore, in summary, the randomized trials in the Cochrane analysis show an improved clinical pregnancy rate and live birth rate of antioxidants versus placebo or no treatment, which is no longer detectable for live birth rate when the trials at high risk for bias were removed. However, because of the multitude of methodological problems in the studies involved and the overall low level of evidence, the authors consider the results of their analysis insufficient to make a recommendation for single agents or combinations of antioxidants and point to the urgent need for further large randomized trials (Smits et al. 2019).

Of the large randomized trials requested, one large study with 174 patients (Steiner et al. 2020) and one very large study with 2370 patients (Schisterman et al. 2020) have now appeared. These multicenter studies were conducted with either a combination of 5 mg folic acid/30 mg zinc or a more complex combination preparation of 500 mg vitamin C, 400 mg vitamin E, 0.20 mg selenium, 1000 mg L-carnitine, 20 mg zinc, 1000 µg folic acid, and 10 mg lycopene. Thus, in total, these two studies alone included more than three times as many patients for the live birth rate analysis as were reported in the Cochrane analysis as a whole. Neither of these two large studies showed an advantage of treatment with antioxidants over placebo in terms of sperm concentration, motility, and morphology or DNA fragmentation. Neither clinical **pregnancy rates** (Steiner et al. 2020) nor **live birth rates** (Schisterman et al. 2020) showed differences between treatment groups.

Therefore, especially considering current study results, the widespread **use of antioxidants in routine clinical practice should be clearly opposed** until large multicenter studies show otherwise.

39.2.3.1 Diets

Investigation of the effect of "healthy diets" on sperm quality is of clinical relevance, although the term "healthy diet" is a highly elastic term and often changing in content.

A recent systematic review examined observational studies with respect to the association of diet and sperm quality or fertility/fecundability (Salas-Huetos et al. 2017). Of the 35 studies included, 31 addressed the effect of specific diets on sperm parameters. Overall, the cohort appears very large with n = 12,672 participants, but the two largest studies already include nearly 9000 men studied (Jensen et al. 2013). The remaining studies split the remaining patient numbers. A cross-sectional study (2013) with approximately 700 healthy participants showed decreased sperm concentrations in men with an increased intake of saturated fatty acids (Jensen et al. 2013). Overall, an inverse association of decreased sperm parameters and intake of **Mediterranean diet** (rich in nutrients such as omega-3 fatty acids, some vitamins and antioxidants, and low in saturated fat) was detected (Salas-Huetos et al. 2017). Intake of fish, seafood, fruits and vegetables, and low-fat milk was positively associated with sperm quality (Mendiola et al. 2009; Eslamian et al. 2012).

In contrast, **high-fat diets, soy products, potatoes, cheese, coffee, and alcohol** were associated with impaired sperm parameters (Salas-Huetos et al. 2017). Whereas another cross-sectional study from Scandinavia with 8344 healthy participants showed that **moderate alcohol consumption does not negatively affect sperm** quality (Jensen et al. 2014). In terms of fecundability, this is reduced when male partners have a high intake of **alcohol, caffeine, and red meat** (Salas-Huetos et al. 2017).

These observations do not currently allow conclusions to be drawn about recommendations in clinical practice, as observational studies reflect associations but not causal relationships. Again, large prospective studies are needed to confirm these findings.

39.2.4 Herbs from Natural Medicine

The literature and evidence on the use of herbs in the treatment of male infertility are very sparse. Review articles are mostly narrative and lack objectivity or are unscientific in structure. Scientific studies/primary articles are mostly conducted on very small cohorts, with often questionable statistical significance.

Articles supporting the use of herbs, often as part of an **Ayurvedic** approach, see benefits of this treatment as including the greater accessibility of these preparations to patients, lower cost, and, underlying the concept, better holistic treatment. Overall, a stimulating effect in terms of libido, vitality, and improved ejaculation is seen through these therapeutic approaches, as well as better nourishment of (sexual) tissues. In a recent review, the following herbs are said to increase sperm count: **polygonatum verticillatum, mucuna pruriens, sesamum indicum** (Dutta and Sengupta 2018). **Studies or statistical evaluations are not listed in this regard**.

At the current time, treatment with herbs from natural medicine to improve sperm quality cannot be recommended due to lack of evidence.

39.2.5 Pentoxifylline /Theophylline

Pentoxifylline is applied as methylxanthine in peripheral circulatory disorders (e.g., intermittent claudication) and is also an inhibitor of phosphodiesterase, as is theophylline. In idiopathic infertility, Pentoxifylline has occasionally been used under the assumption of promoting blood flow to the testes (Heite 1979) without providing convincing evidence of efficacy (Wang et al. 1983; Shen et al. 1991), and few randomized trials have demonstrated improvement in ejaculate parameters compared with placebo, but pregnancy rates or live births were not recorded (Safarinejad 2011).

When used in vitro in the context of IVF treatment, neither Pentoxifyllinenor theophylline clearly demonstrated an increase in fertilization rates in asthenozoospermia, IVF failure, and sperm antibodies (review in Tournaye et al. 1995).

When used in vitro in the context of ICSI treatment with immotile or near-immotile ejaculated sperm or with minimally motile epididymal or testicular sperm, both substances show an improvement in sperm motility as well as fertility and pregnancy rates (review in Oseguera-López et al. 2019) also compared to selection of motile sperm by HOS assay (Mangoli et al. 2011).

39.2.6 Antibiotics and Anti-Inflammatory Drugs

Prior to the widespread use of antibiotics, **obstructions of the seminal ducts due to STDs** or clinical infections of the seminal ducts were the most common cause of male infertility and still are in parts of sub-Saharan Africa (Nieschlag 1993). The gold standard for treatment of clinically manifest infections of the vas deferens is antibiotic treatment depending on the result of the resistogram. If a **resistogram** is not (yet) available, the current guidelines of urologic societies recommend **fluoroquinolones** (e.g., ciprofloxacin, levofloxacin), **macrolides** (e.g., azithromycin), or **tetracyclines** (e.g., doxycycline 100 mg 1-0-1) for 10 to 14 days in first-line treatment (Bonkat et al. 2019).

As indisputable as the antibiotic therapy of symptomatic, clinically manifest infections of the vas deferens is, the antibiotic therapy of sole **leukozoospermia** and/or **nonsignificant germ detection** in asymptomatic subclinical courses is unclear. In asymptomatic leukozoospermia, the current guidelines of the European urological societies recommend an **ejaculate culture** (Jungwirth et al. 2012). However, in an attempt to validate this guideline in asymptomatic infertile patients, there were no differences in the proportion of patients with significant germ detection in patients with and without leukozoospermia, and 80% of positive germ detections were in patients without leukozoospermia (Ventimiglia et al. 2020).

Some of the few randomized trials in infertile men with asymptomatic leukozoospermia or nonsignificant germ detection show improvement in leukozoospermia and ejaculate parameters with antibiotic administration, while others fail to show any effects, as improvements were also detectable in the placebo or nontreated group (Comhaire et al. 1986; Yanushpolsky et al. 1995; Krisp et al. 2003). Therefore, due to the questionable efficacy of **antibiotics** in asymptomatic patients with leukozoospermia or nonsignificant germ detection, antibiotic treatment of these patients **cannot be recommended**, also in view of the potential side effects and development of resistance (Samplaski and Nangia 2015).

One of the main characteristics of infertile men with asymptomatic leukozoospermia or nonsignificant germ detection is **subtotal occlusion** of the seminal ducts with sometimes highly fluctuating ejaculate parameters, which cannot be explained by the abstinence period or the otherwise usual variance of ejaculate parameters. Therefore, to improve patency of the vas deferens, glucocorticoids or nonsteroidal anti-inflammatory drugs have been used in a few small studies. These mainly uncontrolled studies suggest that some positive aspect of the substances is plausible. However, the quality and number of studies are not sufficient for a reliable assessment (For an overview, see Haidl et al. 2019). Compared to treatment with antibiotics, the significantly lower potential for side effects, the rapid onset of action, and the favorable cost of treatment suggest that further evaluation, particularly of **nonsteroidal anti-inflammatory drugs**, is desirable in infertile men with asymptomatic leukozoospermia or nonsignificant germ detection.

39.2.7 Historical Deviations: Mesterolone, Pulsatile GnRH, Kallikrein, etc.

Since spermatogenesis cannot proceed normally without testosterone, therapy of idiopathic infertility with androgens has been attempted again and again, although it cannot be rationally justified, since a clinically relevant androgen deficiency has not been demonstrated in this clinical picture. Nevertheless, **testosterone esters** are repeatedly used in infertility, although they are considered **contraindicated** in existing desire for offspring (see Chap. 36).

Since **mesterolone** hardly suppresses gonadotropins and thus is not thought to have a suppressive effect on spermatogenesis, this androgen has been widely used. Finally, after years of using mesterolone in practice, WHO conducted a large multicenter, randomized, controlled, double-blind study of 246 couples, and it showed no statistically significant increase in pregnancy rate over a placebo (WHO World Health Organization 1989). Further publications followed, so that at least nine randomized, placebo-controlled double-blind studies could be evaluated in a meta-analysis. With

regard to pregnancy rates, the combined odds ratio for 1025 couples was only 1.02. In other words, 359 patients would have to be treated for an additional pregnancy to occur (Kamischke and Nieschlag 1999).

Thus, the **administration of androgens in male infertility is not justified and even contraindicated**. The fact that since 1995, despite the almost exponential increase of placebo-controlled studies in andrology, no additional studies with androgens have been performed underlines this statement.

In preliminary studies, it was hypothesized that oligoasthenoteratozoospermia with elevated FSH levels might be due to an **excessively low GnRH pulse rate**, and the term "slow-pulsing oligospermia" was coined (Wagner and Warsch 1984). In another study, lower LH with normal FSH pulsatility was reported in men with oligozoospermia compared with normal controls (Reyes-Fuentes et al. 1996). An uncontrolled study then demonstrated that such therapy did indeed bring FSH levels into the normal range, but did not demonstrate an improvement in sperm parameters or pregnancy rate (Bals-Pratsch et al. 1989). The hypothesis that the increased FSH levels were the cause and not the consequence of the spermatogenesis disorder could not be confirmed. Due to the lack of a pathophysiological concept and the lack of therapeutic success, a controlled study with this therapeutic substitute did not appear necessary.

There is no clear therapeutic concept for the use of **kallikrein**. Nevertheless, since the 1980s, kallikrein has been used in the treatment of idiopathic fertility disorders, especially to improve spermatozoa motility. In a controlled, randomized, double-blind study of 91 couples, it was demonstrated that kallikrein treatment did not result in significant improvement in seminal parameters and pregnancy rates (Keck et al. 1994). Similar negative results were reported in Japan (Yamamoto et al. 1996). A prospective, placebo-controlled, randomized study conducted in Israel with 114 patients also failed to detect any improvement in seminal parameters (Glezerman et al. 1993). These studies suggest that kallikrein, in the dosage and preparation forms chosen to date, does not show fertility chances of the patient with idiopathic infertility (Vandekerckhove et al. 1996b).

A number of other agents have been used to treat idiopathic male infertility. For example, **bromocriptine,** used successfully for hyperprolactinemia, has been tried for infertility without any positive effects being reported (Vandekerckhove et al. 1996a). Without a clear concept and without convincing data, empirically used substances also include **growth hormone and oxytocin, interferon, mast cell blockers, and antihistamines (ketotifen), angiotensin-converting enzyme (ACE) inhibitors (captopril), and zinc salts.**

Overheating of the genital organs is considered a fertility-reducing factor; **cooling of the scrotal organs** has been variously tried as a therapy. However, a convincing approach to increase pregnancy rates has not yet been developed (Jung and Schuppe 2007).

Acupuncture has also been considered for the treatment of male infertility. However, positive effects on pregnancy rates have not been reported to date (Ng et al. 2008).

39.3 Therapeutic Guideline

The previous sections of this chapter show that drug treatment of idiopathic male infertility is extremely unsatisfactory and that no drug has been clearly demonstrated to be effective. The chapter also emphasizes the **enormous importance of randomized, placebo-controlled clinical trials** in andrology (Kamischke and Nieschlag 1999). This is because only when the effectiveness of a treatment has been demonstrated by a controlled trial should it be generally applied. Until then, the principle applies:

Any therapy for male infertility must be considered experimental until its effectiveness has been demonstrated in randomized controlled trials. Therapeutic interventions without evidence of effectiveness should be used only in clinical trials.

Strict adherence to this principle requires great **discipline** on the part of the treating physicians and **consensus** among the medical profession so that therapies are not used prematurely and pregnancies that would have occurred spontaneously are not attributed to this therapy. The patient made happy by the pregnancy would not see through this placebo effect.

At present, empirical forms of therapy have taken a back seat in view of the success of **assisted fertilization procedures**. In particular, **ICSI treatment** proves beneficial in cases with marked oligoasthenoteratozoospermia and even azoospermia. However, it is precisely through assisted fertilization that previous experience has been proven once again: that intensive therapy of the woman's reproductive functions is also the best treatment of the man's infertility. This should be emphasized in the following principle:

Any therapy of male fertility disorders must be accompanied by optimization of **female reproductive functions**. This principle is also and especially valid if there is no effective therapy on the male side.

However, the lack of success of empirical therapies to date should not discourage the search for effective treatments of male infertility. For despite the successes of assisted reproduction, it remains to be said that most patients would like to conceive their children in a private atmosphere and not in a laboratory, and would therefore prefer a causal therapy for their condition. Moreover, especially in societies where the costs of assisted reproduction are not covered by the community (the insured), there is considerable demand for drugs that are reimbursable or at least cheaper than assisted reproduction. This pressure must not result in hasty prescribing, but must act as a motivation for intensified research. The treating physician has the important and time-consuming task of informing the patient and the couple and guiding them through the jungle of available drugs and procedures. In the absence of a rational therapeutic approach, intensive medical discussion among the physician and his patients remains the measure best leading to the goal, along with optimization of female reproductive functions.

Key Points

- Men with idiopathic infertility represent the largest proportion of patients with unfulfilled desire for children. Due to the lack of etiologic factors, causal therapy is not possible in these patients. Empirical therapy is often used, and here the postulate of Evidence-Based Medicine according to randomized controlled trials proves to be particularly important.
- Treatment with gonadotropins: Recent Cochrane and meta-analyses show a positive effect on pregnancy rates after treatment with gonadotropins. Due to the small number of controlled, randomized studies, no clear recommendation for FSH therapy is possible so far. Here, the pharmacogenetic approach in particular plays an important role; clearer courses of action would be derived by better selection of patients who could potentially benefit from FSH therapy.
- Recent meta-analyses on the use of antiestrogens show a positive impact of therapy on pregnancy rates and individual sperm parameters. However, again, due to the small number of studies and the different statistical methods, a clear recommendation cannot be made. Nevertheless, due to the low side effect profile and low price, antiestrogen treatment can be considered in men with low testosterone.
- Similarly, aromatase inhibitors (AIs) have an effect on testosterone concentration and can be considered in patients with low testosterone and a low T/E2 ratio.
- Antioxidants have a positive effect on DFI and individual ejaculate parameters, although there is considerable heterogeneity between studies. Few studies have looked at the effect on clinical pregnancies; here, no difference has been found between placebo and antioxidants, so their use in routine clinical practice is not recommended.
- The use of antibiotics in asymptomatic patients with leukozoospermia or nonsignificant germ detection cannot be recommended. Treatment with nonsteroidal anti-inflammatory drugs can be considered because of fewer side effects and cheaper costs.
- There is a great deal of momentum in empiric therapy for idiopathic infertility, and the coming years and findings will lead to clearer recommendations for action.
- In any case, therapy for male fertility disorders should be accompanied by optimization of female reproductive functions.

References

Aitken R (1995) Free radicals, lipid peroxidation and sperm function. Reprod Fertil Dev 7:659–668. https://doi.org/10.1071/RD9950659

Appleton J (2002) Arginine: clinical potential of a semi-essential amino acid. Altern Med Rev 7:512–522

Attia AM, Abou-Setta AM, Al-Inany HG (2013) Gonadotrophins for idiopathic male factor subfertility. Cochrane Database Syst Rev 8:CD005071. https://doi.org/10.1002/14651858.CD005071.pub4

Bals-Pratsch M, Knuth U, Hönigl W, Klein HM, Bergmann M, Nieschlag E (1989) Pulsatile GnRH-therapy in oligozoospermic men does not improve seminal parameters despite decreased FSH levels. Clin Endocrinol 30:549–560. https://doi.org/10.1111/j.1365-2265.1989.tb01427.x

Behre HM (2019) Clinical use of FSH in male infertility. Front Endocrinol 10:322. https://doi.org/10.3389/fendo.2019.00322

Bonkat G, Pickard R, Bartoletti R, Cai T, Bruyere F, Geerlings SE, Köves B, Wagenlehner F, Pilatz A, Pradere B, Veeratterapillay R (2019) EAU guidelines on urological infections. Eur Ass Urol:22–26

Branco CS, Garcez ME, Pasqualotto FF, Erdtman B, Salvador M (2010) Resveratrol and ascorbic acid prevent DNA damage induced by cryopreservation in human semen. Cryobiology 60:235–237. https://doi.org/10.1016/j.cryobiol.2009.10.012

Busch AS, Tüttelmann F, Zitzmann M, Kliesch S, Gromoll J (2015) The FSHB c.211G>T variant attenuates serum FSH levels in the supraphysiological gonadotropin setting of Klinefelter syndrome. Eur J Hum Genet 23:700–703. https://doi.org/10.1038/ejhg.2014.142

Cannarella R, La Vignera S, Condorelli R, Mongioì L, Calogero A (2020) FSH dosage effect on conventional sperm parameters: a meta-analysis of randomized controlled studies. Asian J Androl 22:309–316. https://doi.org/10.4103/aja.aja_42_19

Casamonti E, Vinci S, Serra E, Fino MG, Brilli S, Lotti F, Maggi M, Coccia ME, Forti G, Krausz C (2017) Short-term FSH treatment and sperm maturation: a prospective study in idiopathic infertile men. Andrology 5:414–422. https://doi.org/10.1111/andr.12333

Casarini L, Crépieux P, Reiter E, Lazzaretti C, Paradiso E, Rochira V, Brigante G, Santi D, Simoni M (2020) FSH for the treatment of male infertility. Int J Mol Sci 21:2270. https://doi.org/10.3390/ijms21072270

Chua ME, Escusa KG, Luna S, Tapia LC, Dofitas B, Morales M (2013) Revisiting oestrogen antagonists (clomiphene or tamoxifen) as medical empiric therapy for idiopathic male infertility: a meta-analysis. Andrology 1:749–757. https://doi.org/10.1111/j.2047-2927.2013.00107.x

Colagar AH, Marzony ET, Chaichi MJ (2009) Zinc levels in seminal plasma are associated with sperm quality in fertile and infertile men. Nutr Res 29:82–88. https://doi.org/10.1016/j.nutres.2008.11.007

Colpi GM, Francavilla S, Haidl G, Link K, Behre HM, Goulis DG, Krausz C, Giwercman A (2018) European academy of andrology guideline management of oligo-astheno-teratozoospermia. Andrology 6:513–524. https://doi.org/10.1111/andr.12502

Comhaire FH, Rowe PJ, Farley TMM (1986) The effect of doxycycline in infertile couples with male accessory gland infection: a double blind prospective study. Int J Androl 9:91–98. https://doi.org/10.1111/j.1365-2605.1986.tb00871.x

Condorelli RA, La Vignera S, Mongioì LM, Vitale SG, Laganà AS, Cimino L, Calogero AE (2017) Myo-inositol as a male fertility molecule: speed them up! Eur Rev Med Pharmacol Sci 21:30–35

Del Giudice F, Busetto G, De Berardinis E, Sperduti I, Ferro M, Maggi M, Gross M, Sciarra A, Eisenberg M (2020) A systematic review and meta-analysis of clinical trials implementing aromatase inhibitors to treat male infertility. Asian J Androl 22:360–367. https://doi.org/10.4103/aja.aja_101_19

Dorota Halicka H, Zhao H, Li J, Traganos F, Studzinski GP, Darzynkiewicz Z (2012) Attenuation of constitutive DNA damage signaling by 1,25-dihydroxyvitamin D3. Aging 4:270–278. https://doi.org/10.18632/aging.100450

Dutta S, Sengupta P (2018) Medicinal herbs in the management of male infertility. J Preg Reprod 2:1–6. https://doi.org/10.15761/jpr.1000128

Eslamian G, Amirjannati N, Rashidkhani B, Sadeghi MR, Hekmatdoost A (2012) Intake of food groups and idiopathic asthenozoospermia: a case-control study. Hum Reprod 27:3328–3336. https://doi.org/10.1093/humrep/des311

Ferlin A, Vinanzi C, Selice R, Garolla A, Frigo AC, Foresta C (2011) Toward a pharmacogenetic approach to male infertility: polymorphism of follicle-stimulating hormone beta-subunit promoter. Fertil Steril 96:1344–1349. https://doi.org/10.1016/j.fertnstert.2011.09.034

Foresta C, Bettella A, Garolla A, Ambrosini G, Ferlin A (2005) Treatment of male idiopathic infertility with recombinant human follicle-stimulating hormone: a prospective, controlled, randomized clinical study. Fertil Steril 84:654–661. https://doi.org/10.1016/j.fertnstert.2005.03.055

Glezerman M, Lunenfeld E, Potashnik G, Huleihel M, Soffer Y, Segal S (1993) Efficacy of kallikrein in the treatment of oligozoospermia and asthenozoospermia: a double-blind trial. Fertil Steril 60:1052–1056. https://doi.org/10.1016/s0015-0282(16)56409-7

Haidl G, Haidl F, Allam J-P, Schuppe H-C (2019) Therapeutic options in male genital tract inflammation. Andrologia 51:e13207. https://doi.org/10.1111/and.13207

Hankey GJ, Eikelboom JW (1999) Homocysteine and vascular disease. Lancet 354:407–413. https://doi.org/10.1016/S0140-6736(98)11058-9

Heite HG (1979) The effect of Trental on spermiografic parameters, a clinical study in patients with reduced fertility. Fertil Steril 20:38–42

Jensen TK, Heitmann BL, Jensen MB, Halldorsson TI, Andersson AM, Skakkebœk NE, Joensen UN, Lauritsen MP, Christiansen P, Dalgård C, Lassen TH, Jørgensen N (2013) High dietary intake of saturated fat is associated with reduced semen quality among 701 young Danish men from the general population. Am J Clin Nutr 97:411–418. https://doi.org/10.3945/ajcn.112.042432

Jensen TK, Swan S, Jørgensen N, Toppari J, Redmon B, Punab M, Drobnis EZ, Haugen TB, Zilaitiene B, Sparks AE, Irvine DS, Wang C, Jouannet P, Brazil C, Paasch U, Salzbrunn A, Erik Skakkebæk N, Andersson AM (2014) Alcohol and male reproductive health: a cross-sectional study of 8344 healthy men from Europe and the USA. Hum Reprod 8:1801–1809. https://doi.org/10.1093/humrep/deu118

Joshi R, Adhikari S, Patro BS, Chattopadhyay S, Mukherjee T (2001) Free radical scavenging behavior of folic acid: evidence for possible antioxidant activity. Free Radic Biol Med 30:1390–1399. https://doi.org/10.1016/S0891-5849(01)00543-3

Jung A, Schuppe H-C (2007) Influence of genital heat stress on semen quality in humans. Andrologia 39:203–215. https://doi.org/10.1111/j.1439-0272.2007.00794.x

Jungwirth A, Giwercman A, Tournaye H, Diemer T, Kopa Z, Dohle G, Krausz C; European Association of Urology Working Group on Male Infertility. European Association of Urology guidelines on Male Infertility: the 2012 update. Eur Urol. 2012;62(2):324–32. https://doi.org/10.1016/j.eururo.2012.04.048. Epub 2012 May 3. PMID: 22591628.

Kamischke A, Nieschlag E (1999) Analysis of medical treatment of male infertility. Hum Reprod 14:1–23

Kamischke A, Behre HM, Bergmann M, Simoni M, Schäfer T, Nieschlag E (1998) Recombinant human follicle-stimulating hormone for treatment of male idiopathic infertility: a randomized, double-blind, placebo-controlled, clinical trial. Hum Reprod 13:596–603. https://doi.org/10.1093/humrep/13.3.596

Keck C, Behre HM, Jockenhovel F, Nieschlag E (1994) Ineffectiveness of kallikrein in treatment of idiopathic male infertility: a double-blind, randomized, placebo-controlled trial. Hum Reprod 9:325–329. https://doi.org/10.1093/oxfordjournals.humrep.a138501

Knuth U, Hönigl W, Bals-Pratsch M, Schleicher G, Nieschlag E (1987) Treatment of severe oligospermia with human chorionic gonadotropin/human menopausal gonadotropin: a placebo-controlled, double blind trial. J Clin Endocrinol Metab 65:1081–1087. https://doi.org/10.1210/jcem-65-6-1081

Kodama H, Kasai H, Yamaguchi R, Tanaka T, Fukuda J (1997) Increased oxidative deoxyribonucleic acid damage in the spermatozoa of infertile male patients. Fertil Steril 68:519–524. https://doi.org/10.1016/S0015-0282(97)00236-7

Krisp A, Hörster S, Skrzypek J, Krause W (2003) Treatment with levofloxacin does not resolve asymptomatic leucocytospermia—a randomized controlled study. Andrologia 35:244–247. https://doi.org/10.1046/j.1439-0272.2003.00580.x

Lewis SEM, Aitken RJ, Conner SJ, De Iuliis G, Evenson DP, Henkel R, Giwercman GA, Gharagozloo P (2013) The impact of sperm DNA damage in assisted conception and beyond: recent advances in diagnosis and treatment. Reprod Biomed Online 27:325–337. https://doi.org/10.1016/j.rbmo.2013.06.014

Littarru GP, Tiano L (2007) Bioenergetic and antioxidant properties of coenzyme Q10: recent developments. Mol Biotech 37:31–37. https://doi.org/10.1007/s12033-007-0052-y

Mangoli V, Mangoli R, Dandekar S, Suri K, Desai S (2011) Selection of viable spermatozoa from testicular biopsies: a comparative study between pentoxifylline and hypoosmotic swelling test. Fertil Steril 95:631–634. https://doi.org/10.1016/j.fertnstert.2010.10.007

Mendiola J, Torres-Cantero AM, Moreno-Grau JM, Ten J, Roca M, Moreno-Grau S, Bernabeu R (2009) Food intake and its relationship with semen quality: a case-control study. Fertil Steril 91:812–818. https://doi.org/10.1016/j.fertnstert.2008.01.020

Ng EHY, So WS, Gao J, Wong YY, Ho PC (2008) The role of acupuncture in the management of subfertility. Fertil Steril 90:1–13. https://doi.org/10.1016/j.fertnstert.2008.02.094

Nieschlag E (1993) Care for the infertile male. Clin Endocrinol 38:123–133. https://doi.org/10.1111/j.1365-2265.1993.tb00983.x

Oseguera-López I, Ruiz-Díaz S, Ramos-Ibeas P, Pérez-Cerezales S (2019) Novel techniques of sperm selection for improving IVF and ICSI outcomes. Front Cell Dev Biol 7:298. https://doi.org/10.3389/fcell.2019.00298

Padayatty SJ, Katz A, Wang Y, Eck P, Kwon O, Lee JH, Chen S, Corpe C, Levine M, Dutta A, Dutta SK (2003) Vitamin C as an antioxidant: evaluation of its role in disease prevention. J Am Coll Nutr 22:18–35. https://doi.org/10.1080/07315724.2003.10719272

Paradisi R, Busacchi P, Seracchioli R, Porcu E, Venturoli S (2006) Effects of high doses of recombinant human follicle-stimulating hormone in the treatment of male factor infertility: results of a pilot study. Fertil Steril 86:728–731. https://doi.org/10.1016/j.fertnstert.2006.02.087

Pavlovich CP, King P, Goldstein M, Schlegel PN (2001) Evidence of a treatable endocrinopathy in infertile men. J Urol 165:837–841. https://doi.org/10.1016/S0022-5347(05)66540-8

Punab M, Poolamets O, Paju P, Vihljajev V, Pomm K, Ladva R, Korrovits P, Laan M (2017) Causes of male infertility: a 9-year prospective monocentre study on 1737 patients with reduced total sperm counts. Hum Reprod 32:18–31

Raman JD, Schlegel PN (2002) Aromatase inhibitors for male infertility. J Urol 167:624–629. https://doi.org/10.1016/s0022-5347(01)69099-2

Reyes-Fuentes A, Chavarría ME, Carrera A, Aguilera G, Rosado A, Samojlik E, Iranmanesh A, Veldhuis JD (1996) Alterations in pulsatile luteinizing hormone and follicle-stimulating hormone secretion in idiopathic oligoasthenospermic men: assessment by deconvolution analysis—a clinical research center study. J Clin Endocrinol Metab 81:524–529. https://doi.org/10.1210/jcem.81.2.8636262

Safarinejad MR (2011) Effect of pentoxifylline on semen parameters, reproductive hormones, and seminal plasma antioxidant capacity in men with idiopathic infertility: a randomized double-blind placebo-controlled study. Int Urol Nephrol 43:315–328. https://doi.org/10.1007/s11255-010-9826-4

Salas-Huetos A, Bulló M, Salas-Salvadó J (2017) Dietary patterns, foods and nutrients in male fertility parameters and fecundability: a systematic review of observational studies. Hum Reprod Update 23:371–389. https://doi.org/10.1093/humupd/dmx006

Samplaski MK, Nangia AK (2015) Adverse effects of common medications on male fertility. Nat Rev Urol 12:401–413. https://doi.org/10.1038/nrurol.2015.145

Santi D, Granata ARM, Simoni M (2015) FSH treatment of male idiopathic infertility improves pregnancy rate: a meta-analysis. Endocr Connect 4:R46–R58. https://doi.org/10.1530/EC-15-0050

Schisterman EF, Sjaarda LA, Clemons T, Carrell DT, Perkins NJ, Johnstone E, Lamb D, Chaney K, Van Voorhis BJ, Ryan G, Summers K, Hotaling J, Robins J, Mills JL, Mendola P, Chen Z, Devilbiss EA, Peterson CM, Mumford SL (2020) Effect of folic acid and zinc supplementation in men on semen quality and live birth among couples undergoing infertility treatment: a randomized clinical trial. JAMA 323:35–38. https://doi.org/10.1001/jama.2019.18714

Schlegel PN (2012) Aromatase inhibitors for male infertility. Fertil Steril 98:1359–1362. https://doi.org/10.1016/j.fertnstert.2012.10.023

Schubert M, Pérez Lanuza L, Gromoll J (2019) Pharmacogenetics of FSH action in the male. Front Endocrinol 10:47–47. https://doi.org/10.3389/fendo.2019.00047

Selice R, Garolla A, Pengo M, Caretta N, Ferlin A, Foresta C (2011) The response to FSH treatment in oligozoospermic men depends on FSH receptor gene polymorphisms. Int J Androl 34:306–312. https://doi.org/10.1111/j.1365-2605.2010.01086.x

Shen M, Chiang P, Yang R, Hong C, Chen S (1991) Pentoxifylline stimulates human sperm motility both in vitro and after oral therapy. Br J Clin Pharmacol 31:711–714. https://doi.org/10.1111/j.1365-2125.1991.tb05600.x

Simoni M, Casarini L (2014) Mechanisms in endocrinology: Geneticsof FSH action—a 2014-and-beyond view. Eur J Endocrinol 170:91–107. https://doi.org/10.1530/EJE-13-0624

Simoni M, Santi D (2020) FSH treatment of male idiopathic infertility: time for a paradigm change. Andrology 8:535–544. https://doi.org/10.1111/andr.12746

Simoni M, Santi D, Negri L, Hoffmann I, Muratori M, Baldi E, Cambi M, Marcou M, Greither T, Baraldi E, Tagliavini S, Carra D, Lombardo F, Gandini L, Pallotti F, Krausz C, Rastrelli G, Ferlin A, Menegazzo M, Pignatti E, Linari F, Marino M, Benaglia R, Levi-Setti PE, Behre HM (2016) Treatment with human, recombinant FSH improves sperm DNA fragmentation in idiopathic infertile men depending on the FSH receptor polymorphism p.N680S: a pharmacogenetic study. Hum Reprod 31:1960–1969. https://doi.org/10.1093/humrep/dew167

Simoni M, Brigante G, Rochira V, Santi D, Casarini L (2020) Prospects for FSH treatment of male infertility. J Clin Endocrinol Metab 105:dgaa243. https://doi.org/10.1210/clinem/dgaa243

Smits RM, Mackenzie-Proctor R, Yazdani A, Stankiewicz MT, Jordan V, Showell MG (2019) Antioxidants for male subfertility. Cochrane Database Syst Rev 3:CD007411. https://doi.org/10.1002/14651858.CD007411.pub4

Steiner AZ, Hansen KR, Barnhart KT, Cedars MI, Legro RS, Diamond MP, Krawetz SA, Usadi R, Baker VL, Coward RM, Huang H, Wild R, Masson P, Smith JF, Santoro N, Eisenberg E, Zhang H (2020) The effect of antioxidants on male factor infertility: the males, antioxidants, and infertility (MOXI) randomized clinical trial. Fertil Steril 113:552–560. https://doi.org/10.1016/j.fertnstert.2019.11.008

Tournaye H, Devroey P, Camus M, Van der Linden M, Janssens R, Van Steirteghem A (1995) Use of pentoxifylline in assisted reproductive technology. Hum Reprod 10:72–79. https://doi.org/10.1093/humrep/10.suppl_1.72

Traber MG, Atkinson J (2007) Vitamin E, antioxidant and nothing more. Free Rad Biol Med 43:4–15. https://doi.org/10.1016/j.freeradbiomed.2007.03.024

Tremellen K (2008) Oxidative stress and male infertility—a clinical perspective. Hum Reprod Update 14:243–258. https://doi.org/10.1093/humupd/dmn004

Tüttelmann F, Nieschlag E (2009) Nosologie andrologischer Krankheitsbilder. In: Nieschlag E, Behre HM, Nieschlag S (eds) Andrologie, 3rd edn. Springer, Cham, pp 90–96

Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M (2006) Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chem Int 1:1–40. https://doi.org/10.1016/j.cbi.2005.12.009

Vandekerckhove P, Lilford R, Vail A, Hughes E (1996a) Bromocriptine for idiopathic oligo/asthenospermia. Cochrane Database Syst Rev 4:CD000152. https://doi.org/10.1002/14651858.cd000152

Vandekerckhove P, Lilford R, Vail A, Hughes E (1996b) Kinin-enhancing drugs for unexplained subfertility in men. Cochrane Database Syst Rev 4:CD000153. https://doi.org/10.1002/14651858.cd000153

Vandekerckhove P, Lilford R, Vail A, Hughes E (2005) Clomiphene or tamoxifen for idiopathic oligo/asthenospermia (withdrawn paper). Cochrane Database Syst Rev 2015:CD000151. https://doi.org/10.1002/14651858.CD000151

Ventimiglia E, Capogrosso P, Boeri L, Cazzaniga W, Matloob R, Pozzi E, Chierigo F, Abbate C, Viganò P, Montorsi F, Salonia A (2020) Leukocytospermia is not an informative predictor of positive semen culture in infertile men: results from a validation study of available guidelines. Hum Reprod Open 2020:1–6. https://doi.org/10.1093/hropen/hoaa039

Wagner TOF, Warsch F (1984) Pulsatile LHRH-therapy of "slow pulsing oligospermia": Indirect evidence for a hypothalamic origin of the disorder. Acta Endocrinol 105:142–144. https://doi.org/10.1530/acta.0.107s142

Wang C, Chan C-W, Wong K-K, Yeung K-K (1983) Comparison of the effectiveness of placebo, clomiphene citrate, mesterolone, pentoxifylline, and testosterone rebound therapy for the treatment of idiopathic oligospermia. Fertil Steril 40:358–365. https://doi.org/10.1016/S0015-0282(16)47300-0

Whitten SJ, Nangia AK, Kolettis PN (2006) Select patients with hypogonadotropic hypogonadism may respond to treatment with clomiphene citrate. Fertil Steril 6:1664–1668. https://doi.org/10.1016/j.fertnstert.2006.05.042

World Health Organization (1989) Mesterolone and idiopathic male infertility: a double-blind study. World Health Organization Task Force on the Diagnosis and Treatment of Infertility. Int J Androl 12:254–264. https://doi.org/10.1111/j.1365-2605.1989.tb01312.x

Yamamoto M, Katsuno S, Hibi H, Miyake K (1996) The lack of effectiveness of kallikrein in the treatment of idiopathic oligozoospermia: a double-blind, randomized, placebo-controlled study. Jap J Fertil Steril 41:1–6

Yanushpolsky EH, Politch JA, Hill JA, Anderson DJ (1995) Antibiotic therapy and leukocytospermia: a prospective, randomized, controlled study. Fertil Steril 1:142–147. https://doi.org/10.1016/s0015-0282(16)57309-9

Yeung CH, De Geyter C, De Geyter M, Nieschlag E (1996) Production of reactive oxygen species by and hydrogen peroxide scavenging activity of spermatozoa in an IVF program. J Assist Reprod Genet 13:495–500. https://doi.org/10.1007/BF02066531